A Study of Alfuzosin SR in Patients Undergoing Trial without Catheter (TWOC) Following Acute Urinary Retention due to BPH

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CERTIFICATE

This is to certify that this dissertation entitled 'A STUDY OF ALFUZOSIN SR IN PATIENTS UNDERGOING TRIAL WITHOUT CATHETER (TWOC) FOLLOWING ACUTE URINARY RETENTION DUE TO BPH' submitted by Dr.G. VEZHAVENTHAN, appearing for M.Ch (Urology) degree examination in August 2007 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of requirements of the Tamil Nadu Dr. M.G.R Medical University, Chennai. I forward this to the Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India.

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INTRODUCTION

Benign prostatic hyperplasia (BPH), one of the most common diseases of aging men, can be associated with bothersome lower urinary tract symptoms (LUTS) that affect quality of life by interfering with normal daily activities and sleep patterns. The prevalence of histopathologic BPH is age dependent, with initial development usually after 40 years of age. By 60 years of age, its prevalence is greater than 50% and by age 85 is as high as 90%.

Approximately one half of all men who have a histological diagnosis have moderate to severe LUTS. Because long-term data from population-based studies have only recently become available, the risks of developing complications and morbidities from untreated BPH are unclear. For example, despite recent evidence, there is still uncertainty regarding the likelihood that a patient with a specific symptom complex will develop complete urinary retention within a particular time frame. Nonetheless, BPH-associated mortality is rare and serious complications are uncommon.

In contrast, LUTS are bothersome to many patients, and the amount of bother may differ greatly among individuals with the same degree of symptom frequency and severity. Since the impact of LUTS on the patient's quality of life is

highly variable and not directly related to any measurable physiological factors, the patient's perception of the severity of the condition, as well as the degree to which it interferes with his lifestyle or causes embarrassment, should be the primary consideration in choosing therapy

These symptoms impair physiological and functional well-being, and interfere with daily living. Although BPH rarely threatens life, it can contribute to acute urological complications, particularly acute urinary retention (AUR), which is often considered to be the most serious complication of BPH.

AUR is relatively common, painful and distressing for the patient. Early estimates of incidence varied widely, but better estimates now available from population-based studies of men in the community indicate an incidence of 5–25 per 1000 person-years, or 0.5–2.5% per year. The risk is cumulative and increases with age.

AUR is one of the main indications for TURP, reported as the precipitating reason for 25–30% of emergency procedures. After an episode of spontaneous AUR (i.e. not caused by a specific event such as surgery, catheterization or drugs), 15% of patients in one long-term study had another episode of AUR, and 75% had subsequent surgery. The current management of

AUR is to insert a urinary catheter to relieve symptoms, but this can add to the patient's symptoms if UTI develops.

In addition to being uncomfortable for the patient, this is an avoidable risk factor for

blood loss after TURP, should surgery become necessary. A trial without catheter (TWOC) is considered preferable to leaving a catheter in place; success rates of 23–28% have been reported, but significant numbers of patients still require TURP.

The functional symptoms of BPH can be reduced by α-blockers such as tamsulosin,Alfuzocin, which improve flow rates and bladder emptying, and it is thought likely that they also help to reduce bladder outlet resistance by effects on the sympathetic tone of the bladder neck and prostatic stroma. By reducing this resistance, provided the patient retains sufficient detrusor function, α-blockers could help relieve AUR and improve the chances of a successful TWOC.

The optimum duration of treatment with α-blockers has not been fully assessed, and there is controversy about the length of time the catheter should remain in situ for the initial treatment phase. One study suggested that more prolonged use of indwelling catheters has better success rates for TWOC; immediate withdrawal had a 44% success rate compared with 62% if the catheter was left for 7 days.[7]

Acute urinary retention (AUR) is the presenting feature in 23–27% of men undergoing prostatectomy for benign conditions. The increased perioperative mortality and morbidity observed in this group are in part due to an increased risk of sepsis and bleeding associated with urinary catheterization before surgery. It is therefore preferable that patients do not have urinary catheters at the time of prostatic surgery, and hence it is common practice for a patient to undergo a trial without catheter (TWOC) after an administration of an alpha blocker to

patients before a TWOC. The success rate of this TWOC is reportedly 23–28%, with 35% of those who are successful requiring prostatic surgery within 6 months

Alfuzosin is a selective alpha1-adrenoceptor antagonist shown to have functional uroselectivity . It effectively relieves LUTS related to BPO and the sustained-release (SR) formulation has been shown to have a urodynamic effect within 3 hours of first administration. Its good safety profile and rapid onset of action make it appropriate for use before a TWOC following AUR.

There is now good evidence that giving the α-blocker alfuzosin to men with benign prostatic obstruction (BPO) before a trial without catheter (TWOC), after a first episode of acute urinary retention (AUR), significantly improves the chances of a successful return to voiding. Whilst up to 62% of patients will have a successful TWOC after receiving alfuzosin , little is known about the long-term outcome afterward.

Observational studies, conducted before medical therapy for BOO was widely available, provide some insight into what might be expected. In a retrospective study published in 1969, Craigen *et al.* reported that during the 7-year follow-up 80% of 89 men who had presented with AUR caused by BPO required prostatic surgery.[2] Over a decade later, in another retrospective study, Breum *et al.* reported an incidence of surgery of 84% at 5 years within their cohort of 70 patients.[3]

Prospective studies in this area are sparse and often provide a short follow-up of few patients. Klarskov *et al.* reported the longest follow-up to date in a prospective study of 1 year with a surgical intervention rate of 85%; in that study of 228 men with AUR they reported that factors predictive of preserved voiding ability after a successful TWOC were a retained volume of <500 ml, a maximum flow rate of >5 ml/s, and the presence of an event thought to provoke AUR. However, in that study most (75%) patients had a catheter passed to relieve their AUR; this was then removed immediately, rather than allowing a period of catheter drainage. This is an important observation, as it has been reported that the chance of a successful TWOC increases with the duration of catheter drainage.[7]

Despite increased interest in the role of α-blockers for managing AUR there are no published prospective series of long-term outcome after a successful TWOC combined with an α-blocker. We sought to evaluate whether administration of sustained release Alfuzocin improves the outcome of Trial Without Catheter (TWOC) compared to placebo after an episode of acute urinary retention (AUR) caused by Benign Prostatic Hyperplasia (BPH), and further comparing the recorded variables & long-term outcome within patients recruited to a prospective study of the effect of alfuzosin on the outcome of a TWOC.

OBJECTIVES

To evaluate whether administration of sustained release Alfuzocin improves the outcome of Trial Without Catheter (TWOC) compared to placebo after an episode of acute urinary retention (AUR) caused by Benign Prostatic Hyperplasia (BPH), by comparing the numbers of patients who voided successfully after removing their catheter: and further comparing the recorded variables like

Patient age,

Initial catheterization volume after AUR,

Prostate size,

PVR after successful voiding

between those who had a successful TWOC and those who did not and identifying whether they are influencing the success of a trial without catheter (TWOC) and subsequent failure in the follow-up period.

REVIEW OF LITERATURE

BENIGN PROSTATIC HYPERPLASIA

BPH is one of the causes of the LUTS in aging men commonly and, probably incorrectly, referred to as prostatism. Histopathologically, BPH is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate. The observation of new epithelial gland formation is normally seen only in fetal development and gives rise to the concept of embryonic reawakening of the stroma cell's inductive potential (Cunha et al, 1983). The precise molecular etiology of this hyperplastic process is uncertain. The observed increase in cell numbers may be the result of epithelial and stromal proliferation or of impaired programmed cell death leading to cellular accumulation. Androgens, estrogens, stromal-epithelial interactions, growth factors, and neurotransmitters may play a role, either singly or in combination, in the etiology of the hyperplastic process.

Previously held notions that the clinical symptoms of BPH (prostatism) are caused simply by a mass-related increase in urethral resistance are too simplistic. It is now clear that a significant portion of LUTS is the result of age-related detrusor dysfunction. Moreover, bladder outlet obstruction itself may induce a variety of neural alterations in the bladder that contribute to symptomatology. Undoubtedly, the constellations of cellular pathologic processes that give rise to the symptoms of LUTS are far more complex than we currently realize.

REGULATION OF PROSTATE GROWTH

Throughout life, the prostate responds to endocrine signals as it develops, undergoes a rapid phase of growth at puberty, maintains its size, and, then, in some cases, develops an abnormal growth with aging that may result in either benign or malignant disease. The cell kinetics of this process are now being defined in terms of the dynamic interplay between growth-promoting and growth-suppressing factors and how they regulate a cell cycle of DNA synthesis and mitosis while balancing between a cycle of cellular death and apoptosis (see review by Denmeade and colleagues [1996]).

The kinetics and dynamics of cell replication and cell death in the human prostate are now being defined in quantitative numbers (Berges et al, 1995). Isaacs has defined the major step in the interaction of the cell cycle between growth and death. The net balance between the rate of cell growth and cell death maintains the steady-state size of the prostate; it appears to be under hormonal and growth factor control and is age dependent. Resolving the mechanisms that control this normal growth balance is most crucial to understanding the imbalance that occurs in tumor growth. [39]

ACUTE URINARY RETENTION

Acute urinary retention (AUR) is one of the most significant complications or long-term outcomes resulting from BPH for a variety of reasons. It has, in the past, represented an immediate indication for surgery. Between 25% and 30% of men who underwent TURP had AUR as their main indication in older series (Holtgrewe et al, 1989), and, today, most patients failing to void after an attempt of catheter removal still undergo surgery. For this reason alone,

AUR is from an economic as well as a patient viewpoint an important and feared event.

For the patient, it presents as the inability to urinate with increasing pain, eventually a visit to the emergency department, catheterization, follow-up visits to physicians, an attempt at catheter removal, and eventually recovery or surgery, both a painful and a time-consuming process. In older literature, the risk of recurrent AUR was cited as being 56% to 64% within 1 week of the first episode and 76% to 83% in men with diagnosed BPH (Breum et al, 1982; Klarskov et al 1987; Hastie et al, 1990).[3,6,33]

The etiology of AUR is poorly understood. Prostate infection, bladder over distention (Powell et al, 1980), excessive fluid intake, alcohol consumption, sexual activity, debility, and bed rest have all been mentioned (Stimson and Fihn, 1990).

SPONTANEOUS VS PRECIPITATED AUR

From a clinical and prognostic point of view, spontaneous AUR should be separated from precipitated AUR, although this is by no means consistently done in the literature. Precipitated AUR refers to the inability to urinate after a triggering event, such as non–prostate-related surgery, catheterization, anesthesia, ingestion of medications with sympathomimetic or anticholinergic effects or antihistamines, or others.

All other AUR episodes are classified as spontaneous (Roehrborn et al, 1999b, 2000). The importance of differentiating the two types of AUR becomes clear when evaluating the ultimate outcomes of patients. After spontaneous AUR, 15% of patients had another episode of spontaneous AUR and a total of 75% underwent surgery, whereas, after precipitated AUR, only 9% had an episode of spontaneous AUR and 26% underwent surgery (Roehrborn et al, 2000). [23]

THE BLADDER'S RESPONSE TO OBSTRUCTION

Current evidence suggests that the bladder's response to obstruction is largely an adaptive one. However, it is also clear that many of the clinical symptoms of prostatism are related to obstruction-induced changes in bladder function, rather than to outflow obstruction directly. Approximately one third of men continue to have significant voiding dysfunction after surgical relief of obstruction (Abrams et al, 1979). [29]

Obstruction-induced changes in the bladder are of two basic types:

(1) those changes that lead to detrusor instability or decreased compliance, which are clinically associated with symptoms of frequency and urgency, and

(2) those changes associated with decreased detrusor contractility, which are associated with further deterioration in the force of the urinary stream, hesitancy, intermittency, increased residual urine, and (in a minority of cases) detrusor failure.

Acute urinary retention should not be viewed as an inevitable result of this process. Many patients presenting with acute urinary retention have more than adequate detrusor function, with evidence of a precipitating event leading to the obstruction.

Much of our knowledge of the detrusor's response to obstruction is based on experimental animal studies. Limited information is available on the natural history of the human bladder's response to obstruction. Gosling has demonstrated that the major endoscopic detrusor change, trabeculation, is caused by an increase in detrusor collagen (Gosling and Dixon, 1980; Gosling et al, 1980). Severe trabeculation is associated with significant residual urine (Barry et al, 1993), suggesting incomplete emptying may be the result of increased collagen rather than impaired muscle function. Severe trabeculation, however, is seen in fairly advanced disease.

In experimental animal models, the initial response of the detrusor to obstruction is the development of smooth muscle hypertrophy (Levin et al, 1995). It is likely that this increase in muscle mass, although an adaptive response to increased intravesical pressure and maintained flow, is associated with significant intracellular and extracellular changes in the smooth muscle cell that lead to detrusor instability. Obstruction also induces changes in smooth muscle cell contractile protein expression, energy production, and cell-to-cell communication (Levin et al, 1995).

In experimental animal models, unrelieved obstruction is associated with the development of significant increases in detrusor extracellular matrix (collagen) (Levin et al, 1995). This also appears to be the case in the human, although cause-and-effect relationships have not been established (Gosling and Dixon, 1980). In addition to obstruction-induced changes in the smooth muscle cell and extracellular matrix of the bladder, there is increasing evidence that obstruction may modulate neural-detrusor responses as well (Steers et al, 1990; Clemow et al, 2000). Altered neural control of micturition has been noted in aging rats, including reduced bladder contractility, impaired central processing, and altered sensation (Chai et al, 2000).

INCIDENCE OF AUR IN BPH

Older estimates of occurrence of AUR range from 4 to 15 to as high as 130/1000 person-years (calculated by Jacobsen et al, 1997 based on earlier studies [Craigen et al, 1969; Birkhoff et al, 1976; Ball et al, 1981]), which leads to 10-year cumulative incidence rates ranging from 4% to 73%. The self-reported rate of AUR in a cross-sectional study in 2002 Spanish men was 5.1% (Hunter et al, 1996). [2]

During 15,851 person-years of follow-up in the Physicians Health Study, 82 men reported an episode of AUR, for an incidence rate of 4.5/1000 person-years (95% CI, 3.1 to 6.2) (Meigs et al, 1999). Of the 2115 men aged 40 to 79 years in the Olmsted County study, 57 had a first episode of AUR during 8344 person-years of follow-up (incidence, 6.8/1000 person-years; 95% CI, 5.2 to 8.9) (Jacobsen et al, 1997).

The best data from men diagnosed with BPH stem from the PLESS (McConnell et al, 1998). In PLESS, 1376 placebo-treated men with enlarged prostates and moderate symptoms had complete follow-up over 4 years, of which 99 experienced an episode of AUR for a calculated incidence rate of 18/1000 person-years.[16,23]

Although age in community-dwelling men is an important risk factor, in a BPH trial population of men who already are diagnosed with BPH, other factors can be analyzed. In the placebo groups of three 2-year studies (Marberger et al, 2000) and a 4-year study (PLESS) (McConnell et al, 1998; Kaplan et al, 2000; Roehrborn et al, 1999b, 2000), prostate volume, serum PSA, and symptom severity all were predictors of AUR episodes. [23]

INDICATIONS FOR PROSTATECTOMY

The indications for prostatectomy, by either open approach or transurethral resection, include

(1) Refractory urinary retention;

(2) recurrent or persistent urinary tract infections;

(3) significant symptoms from bladder outlet obstruction not responsive to medical therapy;

(4) recurrent gross hematuria of prostatic origin;

(5) renal insufficiency due to BPH; and

(6) bladder calculi secondary to obstruction.

Currently, TURP accounts for over 90% of prostatectomies performed for benign prostatic hyperplasia. [39]

AUR AND SURGERY

Both surgery and AUR represent distinct endpoints in the disease progression of BPH. There are, however, distinct differences. AUR is an outcome mandating management, and surgery is one of the commonly employed management styles. AUR is probably one of the clearer indications for surgery, leaving the treating physician little choice in a patient who failed a trial without catheter. However, most patients undergo surgery not for AUR but for symptoms (Holtgrewe et al, 1989).

Depending on local practice pattern, AUR accounts for 5% to over 30% of the indications for surgery. AUR can be compared with a fracture. It is impossible for the physician during interaction with the patient to increase or decrease the probability for that outcome to occur. Furthermore, once it has occurred, no interaction or consultation can undo it. In contrast, it is easy to see how patients can be influenced in their decision to undergo surgery by the consultation with the physician.

MEDICAL THERAPY FOR BPH

Medical therapies investigated for BPH include α-adrenergic blockers, androgen suppression, aromatase inhibitors, and plant extracts. α-Adrenergic blockers and androgen suppression are important because the safety and efficacy of drugs in these classes have been critically examined, and these drugs are widely prescribed for the treatment of BPH. Plant extracts are also widely used in some parts of the world despite the lack of properly designed clinical trials. Because plant extracts are not classified as drugs, the marketing and claims are

not critically scrutinized by regulatory agencies.

THE IMPACT OF MEDICAL THERAPY

Prior to the 1980s, prostatectomy was the only widely accepted intervention for BPH. The enthusiasm for medical therapy has been supported in part by the limitations of prostatectomy, which include the morbidity of the surgical procedure, failure to consistently achieve a successful outcome, necessity for re treatment, and the suggestion that prostatectomy increases the risk of delayed life-threatening cardiac events (Lepor, 1993). Although medical therapies do not achieve the same level of efficacy as prostatectomy, the attractive features of medical therapy relative to prostatectomy are that clinically significant outcomes are obtained with fewer, less serious and reversible side effects (Lepor, 1993). Because the indication for intervention in the overwhelming majority of patients with BPH is to improve quality of life by relieving symptoms (Mebust et al, 1989), the lower morbidity of medical therapy is of paramount importance in patient-driven treatment decisions.

Medical therapy is currently considered the preferred treatment alternative for those individuals who lack absolute indications for surgery. Because the overwhelming majority of men undergoing TURP lack absolute indications for intervention (Mebust et al, 1989) and prefer non surgical options, the number of prostatectomies performed throughout the world has decreased. [25]

A survey of the U.S. Medicare database revealed that the absolute number of prostatectomies decreased from 250,000 in 1987 to 116,000 in 1996 to 88,000 in 2000 (Health Care Financing Administration, 1997). Similar reductions in TURPs have been reported from France, Canada, Denmark, and Germany (Holtgrewe, 1998).

SELECTING CANDIDATES FOR MEDICAL THERAPY

The ideal candidate for medical therapy should have symptoms that are bothersome and negatively affect quality of life. The finding of a "high" symptom score alone is not a sufficient indication for medical therapy. The symptoms should be sufficiently bothersome that the patient is willing to make a lifetime commitment to medical therapy, providing the drug is effective and adverse experiences are nonexistent or minimal.

Medical therapy should not be offered to individuals presenting with absolute indications for intervention. Individuals presenting with recurrent urinary retention, recurrent urinary tract infections, renal insufficiency, bladder calculi, and recurrent gross hematuria may develop life-threatening consequences from their BPH if it is not managed surgically.

Until properly controlled clinical studies unequivocally demonstrate favorable outcomes, patients presenting with absolute indications should be discouraged from selecting medical therapy. If informed patients are willing to accept potential risks, medical therapy may be offered with a proviso for careful follow-up and future prostatectomy if medical therapy proves ineffective.

PREVENTING BPH WITH MEDICAL THERAPY

A potential role of medical therapy is to prevent the development of BPH or its progression. There are numerous factors limiting the enthusiasm for preventing the development of BPH. The clinical manifestations of BPH are rarely life threatening. Preventative intervention would have to be initiated before the fifth decade of life coinciding with the development of BPH (Partin, 2000). The long-term exposure to drug-induced adverse events and the prohibitive costs are the primary limitations of prevention therapy. In addition,

effective medical and surgical therapy exists when BPH ultimately does become clinically evident.

Because there is no clinical, biochemical, or genetic predictors of BPH development or progression, every male is at risk. The ability to identify those individuals who are predisposed to develop clinical BPH refractory to medical therapy would provide a more compelling rationale for prophylaxis. There is evidence that men with very large prostates are at greater risk for developing urinary retention (Jacobsen et al, 1997) [15] and that medical therapy (finasteride) can significantly decrease this risk of developing urinary retention (McConnell et al, 1998). The decision to offer preventative therapy for urinary retention depends on the risk of the events, cost associated with treatment, and patient preferences for intervention. [16]

RATIONALE FOR USING α -ADRENERGIC BLOCKERS

The rationale for α-adrenergic blockers in the treatment of BPH is based on the hypothesis that the pathophysiology of clinical BPH is in part caused by BOO, which is mediated by α1 adrenoceptors (α1 AR) associated with prostatic smooth muscle (Caine, 1986). The importance of this dynamic obstruction was supported by morphometric studies demonstrating that smooth muscle is one of the dominant cellular constituents of BPH, accounting for 40% of the area density of the hyperplastic prostate (Shapiro et al, 1992).

Caine and coworkers (1975) reported that the human prostate contracts in the presence of the α-adrenergic agonist norepinephrine.[17] Several investigators subsequently demonstrated that the tension of prostate smooth muscle is mediated by the α1 AR (Hieble et al, 1985; Lepor et al, 1988; Gup et al, 1989). Lepor and Shapiro (1984) were the first investigators to characterize the α1 AR in the human prostate using radioligand binding studies.

These investigators subsequently reported that 98% of the α1 ARs are localized to the prostatic stroma (Kobayashi et al, 1993). The importance of the adrenergic innervation of the prostate was further supported by the observation of high levels of norepinephrine in the human prostate (Lepor et al, 1990).

Although the finding of high levels of smooth muscle α1 ARs and norepinephrine in the human prostate suggests an important role of the adrenergic innervation in prostatic function, it cannot be assumed that these factors are

directly responsible for clinical BPH. Lepor and associates (1990) reported no significant differences between norepinephrine levels, α1 AR density (Gup et al, 1989), or isometric contractile responses to phenylephrine (Gup et al, 1989) in BPH tissues obtained from men with symptomatic and asymptomatic BPH. Other investigators have shown α1 AR levels are higher in prostatic adenoma relative to prostatic capsule (Yamada et al, 1987; Kawabe et al, 1990).

These observations simply show regional differences of α1 AR receptors in the prostate and do not prove that clinical BPH is caused by up-regulation of the α1 AR.The most definitive evidence that blockade of prostate α1 AR relieves BOO was the observed direct relationship between the area density of prostate smooth muscle and the change in the PFR in 26 subjects undergoing prostatic biopsy before initiating α-blocker therapy with terazosin (Shapiro et al, 1992).

Although the prostates of those subjects achieving symptom improvement had a significantly greater group mean area density of smooth muscle compared with those of non responders, a direct relationship between prostate smooth muscle area density and change in symptom scores was not observed. These observations suggest that non prostate smooth

muscle–mediated α1 AR events may also be responsible for the effectiveness of α blockade and that α1-mediated symptom improvement and decreases in BOO are mediated by different mechanisms.

CLASSIFICATION OF ALPHA ADRENERGIC BLOCKERS

α-Adrenergic blockers may be classified according to α AR selectivity and serum elimination half-life. Phenoxybenzamine, a nonselective α blocker, was shown to be highly effective for BPH (Caine et al, 1976, 1978). [17]The limitation of phenoxybenzamine was the high incidence and severity of adverse clinical events.

Berthelson and Pettinger (1977) described two subtypes of α AR (α1 and α2). Prazosin was one of the first α1 AR antagonists to be investigated for the treatment of BPH (Hedlund et al, 1983). The efficacy of phenoxybenzamine and prazosin are comparable; however, prazosin is better tolerated, implying that efficacy and toxicity are mediated primarily by the α1 AR and α2 AR, respectively (Lepor, 1989). Prazosin and other α1 antagonists, including intermediate-release (IR) alfuzosin (Jardin et al, 1991) and indoramin (Ramsay et al, 1985), require at least twice-daily dosing, owing to the relatively short serum elimination half-lives.

The next advance in the development of α blockers was the development of drugs with serum elimination half-lives that allowed for once-a-day dosing. Terazosin (Lepor et al, 1992) and doxazosin (Gillenwater et al, 1995) are long-acting α blockers that have been shown to be safe and effective for the treatment of BPH.

Molecular cloning studies have identified three subtypes of the α1 AR (Andersson et al, 1997). Price and coworkers (1993) reported that the mRNA encoding the α1a AR is predominant in the human prostate. The fact that the α1a mRNA is translated does not mean the encoded protein is translated. Lepor and associates reported that using autoradiographic

(Kobayashi et al, 1993) and immunohistochemical (Walden et al, 1997) techniques, the α1a AR and α1b AR are predominant in the human stroma and epithelium, respectively. Prostate smooth muscle tension has been shown to be mediated by the α1a AR (Forray et al, 1994a and b).

This observation is consistent with the localization of the α1L AR to prostatic stroma. Muramatsu and colleagues (1994) subsequently reported that the α1L AR was present in the prostate and mediated prostate smooth muscle contraction. The overwhelming evidence to date suggests that the α1L AR binding site is a conformational state of the α1a AR (Andersson et al, 1997).

Tamsulosin is a once-daily administered α1 antagonist that exhibits some modest degree of selectivity for the α1a versus the α1b AR and no selectivity for the α1a versus the α1d AR (Foglar Of all of the other factors examined only the post void residual volume (PVR) after a successful TWOC approached statistical significance, those with residuals of > 50 ml being more likely to fail during the follow-up. The pharmaceutical industry has developed α1 antagonists that are 1000-fold selective for the α1a AR versus α1b/α1d (Forray et al, 1994b). Because the α1 AR subtypes mediating efficacy and adverse effects are unknown, the optimal specific α1 AR subtype antagonist for the treatment of BPH cannot be predicted (Lepor, 1996). The clinical use of these highly selective α1AR antagonists will be defined by future clinical trials.

ALFUZOSIN

IR alfuzosin was investigated for the treatment of BPH primarily in Europe in the early 1990s. Jardin and colleagues (1991) reported the first large-scale, multicenter, randomized, placebo-controlled trial demonstrating that alfuzosin was safe and effective for the treatment of

BPH. A long-term open-label extension study showed that the effectiveness of alfuzosin was durable up to 30 months (Jardin et al, 1994). The primary limitation of IR alfuzosin was a requirement for multiple daily doses (2.5 mg three times a day or 5 mg twice a day). In the absence of any demonstrable advantage over the once-a-day drugs like terazosin, doxazosin, and tamsulosin, there was no compelling reason to prescribe IR alfuzosin.

SR ALFUZOSIN

SR alfuzosin is a new formulation that allows for a once-daily dosing regimen without dose titration. SR alfuzosin is not currently registered in the United States. Buzelin and coworkers (1997) reported the first randomized, multicenter, placebo-controlled trial evaluating the safety and effectiveness of SR alfuzosin for the treatment of BPH. Three hundred and ninety subjects were randomized to once-daily 5 mg alfuzosin versus placebo for 12 weeks. The treatment-related improvements in the IPSS and PFR were -1.6 symptom unit and 1.3 ml/sec, respectively. The incidence of dropouts because of adverse events was 4.6% and 7.1% in the SR alfuzosin and placebo groups, respectively. The 2-mm Hg change in systolic and diastolic blood pressure was not significantly different from that in the placebo group. The incidences of dizziness and asthenia were similar in the SR alfuzosin and placebo groups.

SR alfuzosin (10 mg once a day) has been compared with IR alfuzosin (2.5 mg three times daily) and placebo (van Kerrenbroeck et al, 2000). After a 1-month placebo lead-in, 447 patients were randomly assigned in equal proportions to the three treatment groups for 3 months. The improvement in the IPSS was 6.9, 6.4, and 4.9 in the alfuzosin 10 mg/day, alfuzosin 2.5 mg three times a day, and placebo groups, respectively. The symptom improvement observed in both active treatment groups was significantly greater than that in the

placebo group. The improvements in the filling and voiding subscores and quality of life index were also significantly greater in the active treatment group relative to the placebo group.

The improvement in the PFR was 2.3 ml/sec, 3.2 ml/sec, and 1.4 ml/sec in the SR alfuzosin, IR alfuzosin, and placebo groups, respectively. The modest improvements in the PFR were significantly greater in both active treatment groups compared with placebo. The incidences of dizziness were 2.1%, 4.7%, and 1.3%; and those for asthenia were 3.5%, 0.7%, and 2.6% in the SR alfuzosin, IR alfuzosin, and placebo groups, respectively.

No sexual dysfunction was reported in the 10-mg/day alfuzosin group. There were no statistically or clinically significant treatment-related effects on blood pressure in normotensive or hypertensive subjects. Of those men who were hypertensive at baseline, the mean reductions in the standing blood pressure were 8.1, 8.6, and 5.8 mm Hg, respectively, in the SR alfuzosin, IR alfuzosin, and placebo groups. The lack of adverse events and meaningful blood pressure effects appears to be the distinguishing characteristic of SR alfuzosin compared with terazosin and doxazosin.

Because of the lack of adverse effects and blood pressure changes, alfuzosin has been promoted as an uroselective drug (Kirby, 1998a). SR alfuzosin exhibits no pharmacologic uroselectivity for any of the α1 subtypes (Andersson et al, 1997). In vivo studies in the conscious rat have shown that alfuzosin reduces urethral pressure without significantly altering blood pressure (Martin et al, 1995). This experimental observation does not prove clinical uroselectivity because terazosin and doxazosin do not alter blood pressure in normotensive subjects. Another explanation for the lack of adverse events has been the low penetration of alfuzosin into the brain (Rouguier et al, 1994).

It is also important to consider that the better tolerance may simply be related to a lower

level of α1 blockade because the treatment-related improvement of the 10 mg of alfuzosin appears to be less than that achieved with 10 mg of terazosin and 8 mg of doxazosin.

The long-term effectiveness of IR alfuzosin 2.5 mg three times a day is supported by an open-label prospective 3-year trial involving 3228 men with clinical BPH (Lukacs et al, 2000). The improvements in symptom score in BPH-specific health-related quality of life index observed at the 3-month visit were maintained throughout the 36 months of follow-up. A total of 20.1% of the men withdrew from the study. Only 4.2% of the men discontinued therapy because of an adverse event. The other reasons for withdrawal were death, 7.6%; loss of follow-up, 1.7%; lack of efficacy, 1.8%; study withdrawal owing to personal reasons, 0.8%; concomitant disease, 0.7%; and other reasons, 3.3%. Only 0.3% of men experienced acute urinary retention. It is reasonable to assume that the SR alfuzosin also exhibits durability of effectiveness.

EFFECTS OF ALPHA BLOCKERS ON BOO

The primary objective of medical therapy is to improve urinary symptoms. The relevance of urodynamic studies for assessing the clinical use of medical therapy for BPH is controversial. A drug that improves urodynamic parameters of BOO without relieving LUTS would be of limited clinical utility. Conversely, a drug that relieves LUTS without improving urodynamic parameters of BOO would be of great clinical importance. There are relatively few randomized, placebo-controlled studies examining the effects of α blockers on pressure-flow parameters. One of the limitations to designing these urodynamic studies is the definition of a clinically significant outcome.

Martorana and colleagues (1997) reported a randomized, double-blind, placebo-controlled study examining the effect of 1 month of alfuzosin, 2.5 mg three times a day, on

pressure-flow urodynamic parameters. The changes in detrusor pressure at maximum flow, detrusor opening pressure, and maximum detrusor pressure were significantly greater in the alfuzosin-treatment group compared with the placebo group. There were no significant differences between the effects of alfuzosin and those of placebo on PFR.

SR ALFUZOSIN IN ACUTE URINARY RETENTION

It is reasonable to speculate that urinary retention is caused in part by dynamic factors because a significant proportion of men void spontaneously after catheter placement (Taube and Gajraj, 1989). If urinary retention is caused by increased sympathetic activity at the level of the prostatic smooth muscle, an α blocker should increase the likelihood of spontaneous voiding after catheter removal. [4]

The advantage of SR alfuzosin and tamsulosin over terazosin and doxazosin in the management of acute urinary retention is that a therapeutic dose can be administered at the onset of treatment, thereby decreasing the time for attempting catheter removal.

A large-scale, randomized, double-blind, placebo-controlled, trial of long-term duration is required to determine whether a medical therapy prevents urinary retention. Unfortunately, no randomized, double-blind, placebo-controlled studies of α blockers exceed 1 year of active treatment. Because men with large prostates have a threefold greater chance of developing urinary retention (Jacobsen et al, 1997), enrolling men with large prostates would enhance the probability of observing an effect on urinary retention. The 3-year open-label prospective study of alfuzosin supported a 0.3% risk of retention (Lukacs et al, 2000). This is markedly lower than the predicted risk of developing urinary retention in an age-matched cohort of men (Jacobsen et al, 1997). [15]

The MTOPS study is a 7-year placebo-controlled trial of 2800 men designed to

determine the impact of medical therapy (placebo, doxazosin alone, finasteride alone, and combination therapy) on disease progression. This study will determine the impact of α blockers on preventing urinary retention.

ADVERSE EVENTS WITH ALPHA BLOCKERS

Dizziness and asthenia are the adverse events most commonly associated with α blocker therapy. Elucidating the mechanism of action for these adverse events is essential for α1 subtype drug development programs. It has been assumed that dizziness and possibly asthenia were caused by cardiovascular effects. Lepor and colleagues (2000) correlated the incidence of adverse events associated with terazosin relative to blood pressure changes. Men experiencing dizziness and asthenia did not exhibit greater changes in blood pressure while on terazosin therapy. Only postural hypo tension was associated with greater changes in blood pressure.

Alpha 1-Adrenergic–mediated dizziness and asthenia are likely due to effects at the level of the CNS. Therefore, it cannot be assumed that developing an α blocker that eliminates effects on blood pressure will significantly improve the tolerability of α blockers.

COMPARISON OF ALPHA ADRENERGIC BLOCKERS

Buzelin and coworkers (1997a) reported a randomized, placebo-controlled study comparing α blockers (IR alfuzosin, 2.5 mg three times a day, versus tamsulosin, 0.4 mg/day). The improvements in Boyarsky symptom score and PFR and the incidences of dizziness and asthenia were not significantly different between the two treatment groups. The effects of alfuzosin and tamsulosin on systolic and diastolic supine or standing blood pressures in the hypertensive patients were also not significantly different. This study suggests that IR alfuzosin and tamsulosin have equivalent effectiveness and tolerability. The obvious benefit of

tamsulosin is that the dose does not have to be titrated.

The recommended daily doses of terazosin, doxazosin, tamsulosin, and SR alfuzosin are 10 mg, 8 mg, 0.4 mg, and 10 mg, respectively. The clinical data suggest that terazosin, 10 mg, and doxazosin, 8 mg, are more effective than tamsulosin, 0.4 mg, and alfuzosin, 10 mg. The incidences of asthenia and dizziness appear to be higher for terazosin and doxazosin. The apparent better tolerability of tamsulosin and SR alfuzosin may simply be because of degree of α1 blockade and not uroselectivity.

Terazosin and doxazosin exhibit very similar pharmacological and pharmacokinetic properties. It is, therefore, not surprising that the effectiveness and tolerability of these two agents are also comparable. The effectiveness of terazosin and doxazosin are both dose dependent, with the greatest recorded improvements in symptom scores observed at the 10-mg and 8-mg daily doses, respectively. These doses have both been shown to be significantly more effective than lower doses. Although the incidence of adverse events is dose dependent, the 10-mg and 8-mg doses of terazosin and doxazosin are generally well tolerated.

Tamsulosin and SR alfuzosin have been positioned as uroselective α1 blockers. One of the assumed advantages of a uroselective α1 blocker is better tolerance. Whereas the 0.8-mg tamsulosin dose appears to have less asthenia than terazosin and doxazosin, the incidence of dizziness is comparable and rhinitis and abnormal ejaculation are markedly greater. Tamsulosin, 0.4 mg, is the only reasonable dose, owing to the cost and adverse events associated with the 0.8-mg dose.

The major advantage of 0.4 mg of tamsulosin and SR alfuzosin is the lack of requirement for dose titration. For men presenting in urinary retention, tamsulosin and SR alfuzosin will likely decrease the time to voiding trial because of the lack of titration to an

effective dose. The data suggest that tamsulosin and SR alfuzosin exhibit less effect on blood pressure in hypertensive men compared with terazosin and doxazosin. The fact that terazosin and doxazosin lower blood pressure in men who are hypertensive may be an advantage, especially because 30% of men with BPH have hypertension.

TWOC AND ALFUZOCIN

Acute urinary retention (AUR) is the presenting feature in 23–27% of men undergoing prostatectomy for benign conditions. The increased perioperative mortality and morbidity observed in this group are in part due to an increased risk of sepsis and bleeding associated with urinary catheterization before surgery. It is therefore preferable that patients do not have urinary catheters at the time of prostatic surgery, and hence it is common practice for a patient to undergo a trial without catheter (TWOC). The success rate of this TWOC is reportedly 23–28%, with 35% of those who are successful requiring prostatic surgery within 6 months

If urinary retention is caused by increased sympathetic activity at the level of the prostatic smooth muscle, an α blocker should increase the likelihood of spontaneous voiding after catheter removal. McNeill and coworkers (1999) examined the effects of SR alfuzosin, 5 mg twice a day, versus placebo in men presenting with acute urinary retention. The indwelling urinary catheter was removed 24 hours after initiation of treatment. Men were excluded if the bladder volume at the time of catheter drainage was greater than 1.5 liters. Fifty-five percent and 29% of men randomized to the SR alfuzosin and placebo groups voided spontaneously after catheter removal, respectively. The clinical effect was greatest in younger men. Of the men who successfully completed the voiding trial, 32% ultimately experienced a second episode of acute urinary retention or underwent prostatectomy. [36,40]

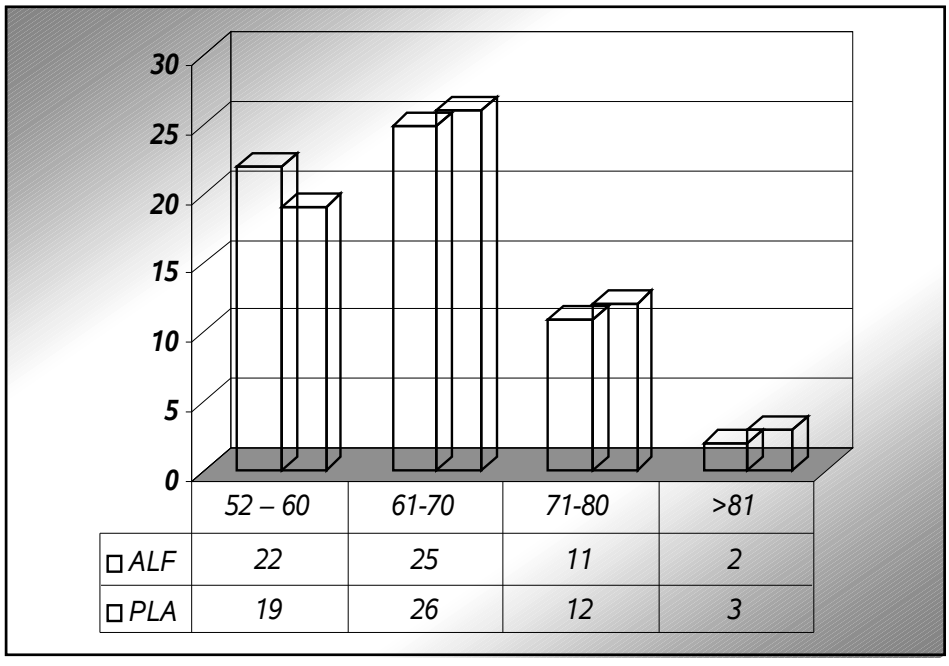
The advantage of SR alfuzosin and tamsulosin over terazosin and doxazosin in the management of acute urinary retention is that a therapeutic dose can be administered at the onset of treatment, thereby decreasing the time for attempting catheter removal.

Alfuzosin is a selective alpha1-adrenoceptor antagonist shown to have functional uroselectivity. It effectively relieves LUTS related to BPO and the sustained-release (SR) formulation has been shown to have a urodynamic effect within 3 hours of first administration. Its good safety profile and rapid onset of action make it appropriate for use before a TWOC following AUR. There is now good evidence that giving the α-blocker alfuzosin to men with benign prostatic obstruction (BPO) before a trial without catheter (TWOC), after a first episode of acute urinary retention (AUR), significantly improves the chances of a successful return to voiding.

PATIENTS AND METHODS

Between December 2004 and October 2006, 120 men aged 52–83 years (mean 64.3) presented with AUR related to Benign Prostatic Hyperplasia and a residual urine volume of 0.5–1.5 L on catheterization were enrolled in a prospective, randomized, double-blind, placebo-controlled study, and randomly assigned to receive SR alfuzosin 10mg once daily (60 patients) or placebo (60 patients): the intent-to-treat (ITT) population was 120 patients. All had been admitted to hospital through the Accident and Emergency Department with AUR, and had been catheterized in the previous 72 hours.

AGE GROUPS



	52 – 60	61-70	71-80	>81
ALF	22	25	11	2
PLA	19	26	12	3

After catheterization the drained volume of urine (residual volume of AUR), size of prostate (assessed by a DRE & abdominal USG) and study number were recorded on a standard case-report form. As a TRUS estimate of prostate size was not available for this study the admitting urologist was asked to categorize the prostate as small (≤20 g), medium (21–50 g) or large (≥51 g). Serum was sent for assay of serum creatinine, and urine routine examination was done and a sample sent for urine culture. The time and date of commencement of trial medication and catheter removal were also recorded.

Men with initial catheterization volumes of >1500 ml or <500 ml were excluded. Other exclusion criteria are evidence of renal or hepatic dysfunction; previous surgery on the urinary tract; other diseases of the bladder; any malignancy; retention-enhancing medications; allergies; and severe cardiac disease. The exclusion criteria are listed separately in the next page.

Full informed written consent was sought from eligible patients. Those who gave consent were randomly allocated to receive either SR alfuzosin (10 mg once daily, with no dose titration) or placebo once daily for 7 days (7 doses).. The catheter was removed after 24 h of the full course of medication. We packaged the SR alfuzosin and placebo to appear identical and each batch of seven tablets was allocated a study number generated randomly by computer. A sealed copy of the code was held by the investigator.

SUCCESS

In the absence of any internationally agreed outcome measures for the success of a TWOC, TWOC was considered successful if the patient returned to satisfactory voiding (defined as a flow rate of > 5 ml/s, >125 ml voided volume, and a residual volume of ≤ 250 ml). These definitions are regarded as a reasonable reflection of successful bladder emptying; and deemed a failure if re-catheterization was required within 24 hours.

FOLLOW-UP

The patients were then followed to the time of prostatic surgery for some other indication other than AUR or re-catheterization due to recurrent AUR while those who continued to void remained under open follow-up. The failures during follow-up of patients who had a successful TWOC were defined as a subsequent occurrence of AUR and/or of bladder outlet surgery.

EXCLUSION CRITERIA:

- Patients unwilling to give informed consent.
- Significant renal and/or hepatic disease; depressive illness on medication;
- Neurological diseases, e.g. multiple sclerosis, spinal injury; confirmed or suspected urethral stricture.
- UTI, acute or chronic prostatitis.
- History of prostatic or bladder neck surgery.
- Carcinoma of the prostate suspected or confirmed.
- History of unstable angina pectoris, myocardial infarction, transient ischaemic attacks, Cerebrovascular accident or congestive cardiac failure during the previous 6 months; Current or previous orthostatic hypotension (decrease of > 20 mmHg of systolic or diastolic blood pressure).
- Patients taking monoamine oxidase inhibitors, cholinergic or anticholinergic drugs, calcium-channel blockers, or α-blocking drugs. Other antihypertensive drugs not to be altered whilst the patient receives the trial medication.

- Known hypersensitivity to alfuzosin or α-blockers.
- Patients requiring suprapubic catheterization where urethral catheterization was unsuccessful.
- Retention after major abdominal/pelvic surgery.
- Large PVR (>1.5 L).
- Clot retention secondary to haematuria of any cause.

PATIENT PROFORMA

1. Name:

2. Serial Number:

3. Age:

4. Urine volume after Catheterization:

5. Prostate Size on DRE & USG:

6. Investigations:

    Urine routine:

    Urine Culture:

    Sr.Creatinine :

7. Date of starting first dose:

8. Adverse Effects:

9. TWOC (Success/Failure):

10. PVR if voided successfully:

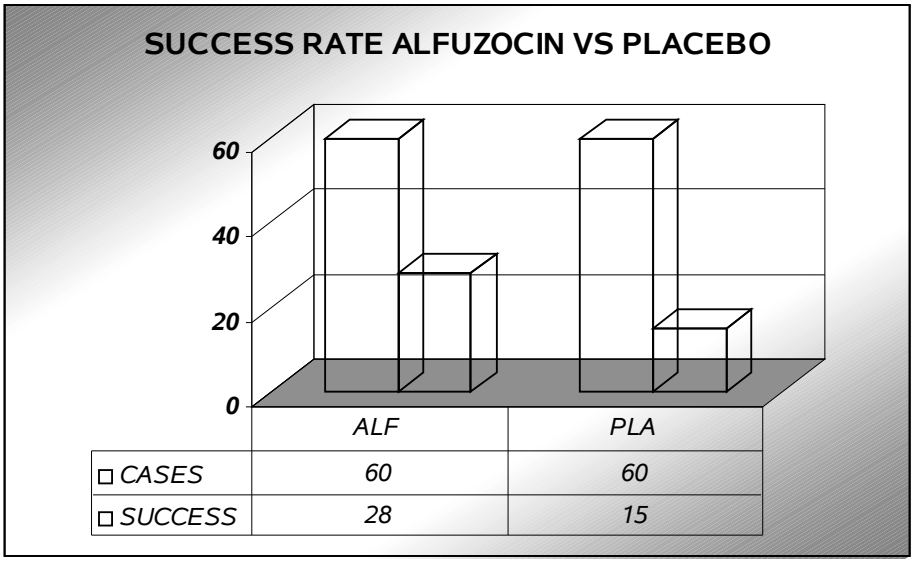
11. Follow-up Duration:

12. Follow-up Result:

OBSERVATION AND RESULTS

Of the 120 patients recruited, 60 received SR alfuzosin and 60 placebo. All variables like patient age, prostate size and residual volume of AUR were comparable in both treatment groups. Two patients in each group gave a history of constipation, which was treated appropriately and was not found to influence the outcome.

After removing the catheter, voiding was successful in 28 of the 60 patients (47%) receiving SR alfuzosin and in 15 of the 60 patients (25%) receiving placebo, the difference being statistically significant (P=0.014). This translates into an odds ratio of 2.63 (95% CI 1.13–6.24).Remaining patients were either not able to pass urine satisfactorily or required re-catheterization within 24 hours.

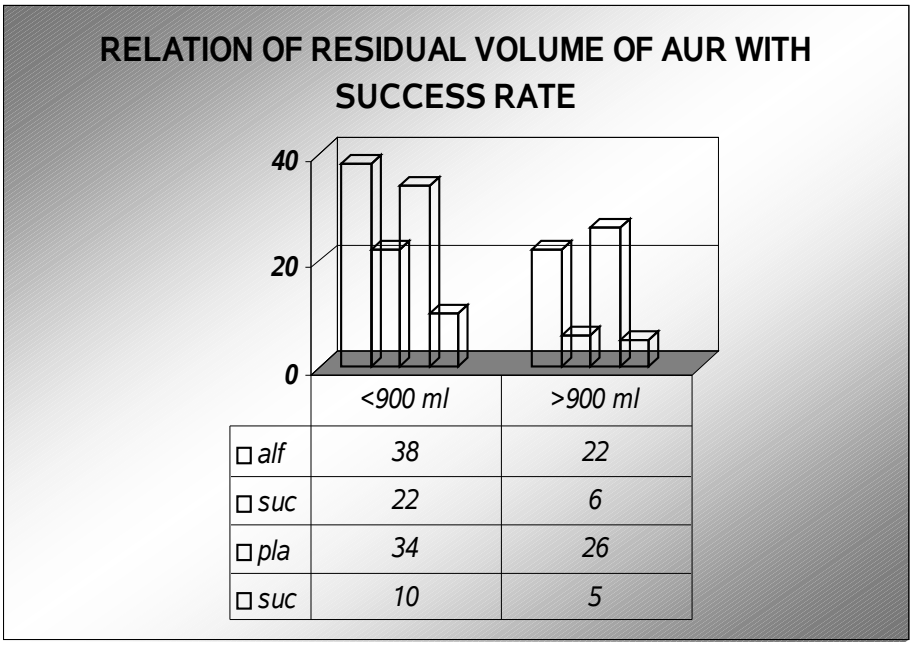


P Value – 0.014 odds ratio 2.63

Comparing the recorded variables between those who had a successful TWOC and those who did not, regardless of treatment group, revealed that age significantly influenced the outcome. Those who had a successful TWOC were a mean of 5.5 years younger than those who failed to void (P=0.015). The difference in favour of younger patients was more pronounced within the placebo group.

The volume of urine after initial catheterization (Residual volume of AUR) has been reported to affect the chances of a successful return to voiding. 22 cases out of 38 in the

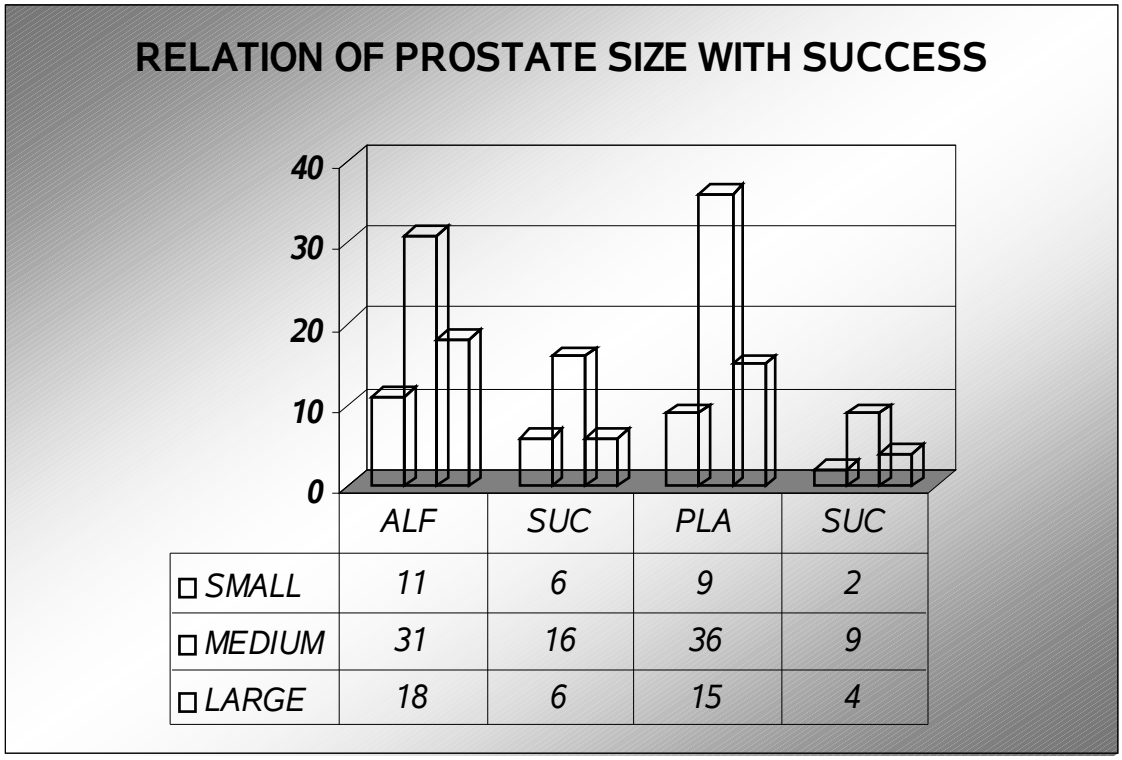
Alfuzocin group and 10 out of 34 in the placebo group with residual volume of AUR <900 ml successfully voided in TWOC. But only 6 cases out of 22 in the Alfuzocin group and 5 cases out of 26 in the placebo group with urine volume after initial catheterization >900 ml were successful in TWOC.This translate into odds ratio of 2.69 (95% CI 1.14 - 6.64) and P value is 0.02 which is statistically significant. Patients with residual volumes of >1.5 L were excluded from the present study.



P Value – 0.02 odds ratio – 2.69

There was no difference in outcome that could be related to prostate size in the present study, possibly because prostate size was assessed by a DRE & abdominal USG in the emergency context, which is much less reliable than TRUS. Number of successful cases in

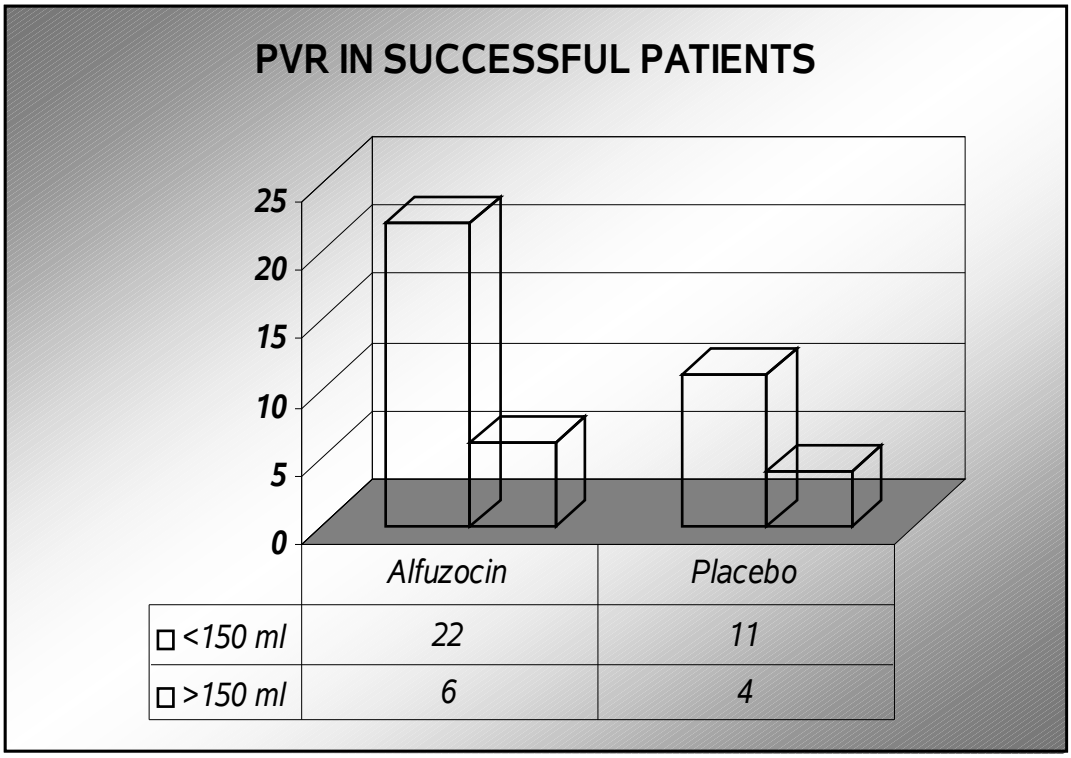
relation to prostate size is given in the table below. Here the P value is 0.72 and so it is statistically insignificant



	ALF	SUC	PLA	SUC
SMALL	11	6	9	2
MEDIUM	31	16	36	9
LARGE	18	6	15	4

P Value – 0.72

Postvoid residual volume (PVR) was assessed by ultrasonography for those who had a successful TWOC. Among those 43 patients who voided successfully, 6 cases in the Alfuzocin group & 4 in the placebo group had PVR > 150 ml. Remaining 33 patients had PVR <150 ml. There was no correlation between the residual volume of the AUR and the PVR after a successful TWOC.



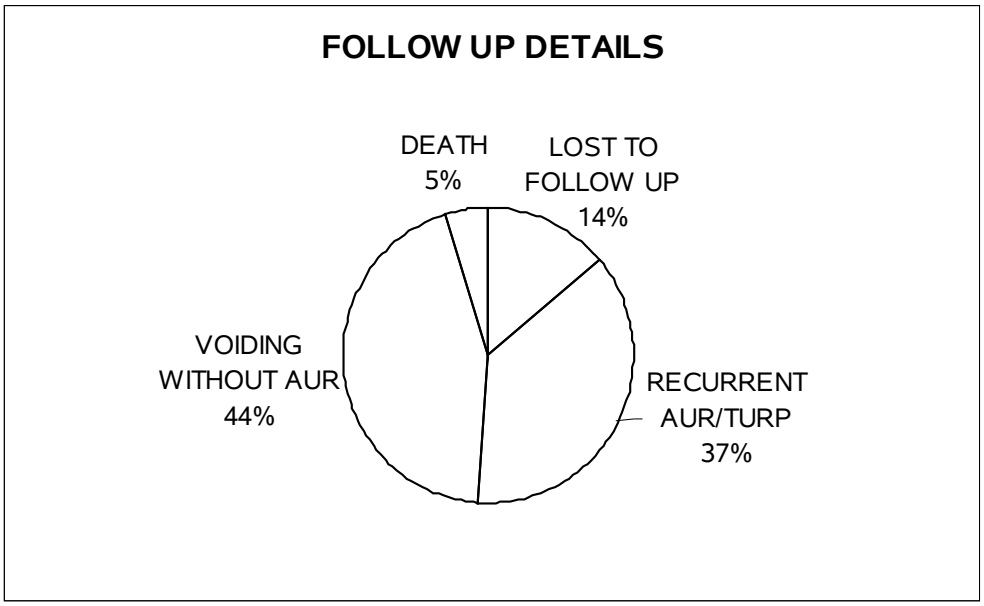
Elderly patients (70 years or older) and patients with a drained volume of 900 ml or greater had significantly greater chances of TWOC failure. Nevertheless, even in the presence of these 2 factors 10 mg alfuzosin once daily almost doubled the likelihood of successful TWOC. . No other factors were significantly different between the outcome groups.

ADVERSE EVENTS

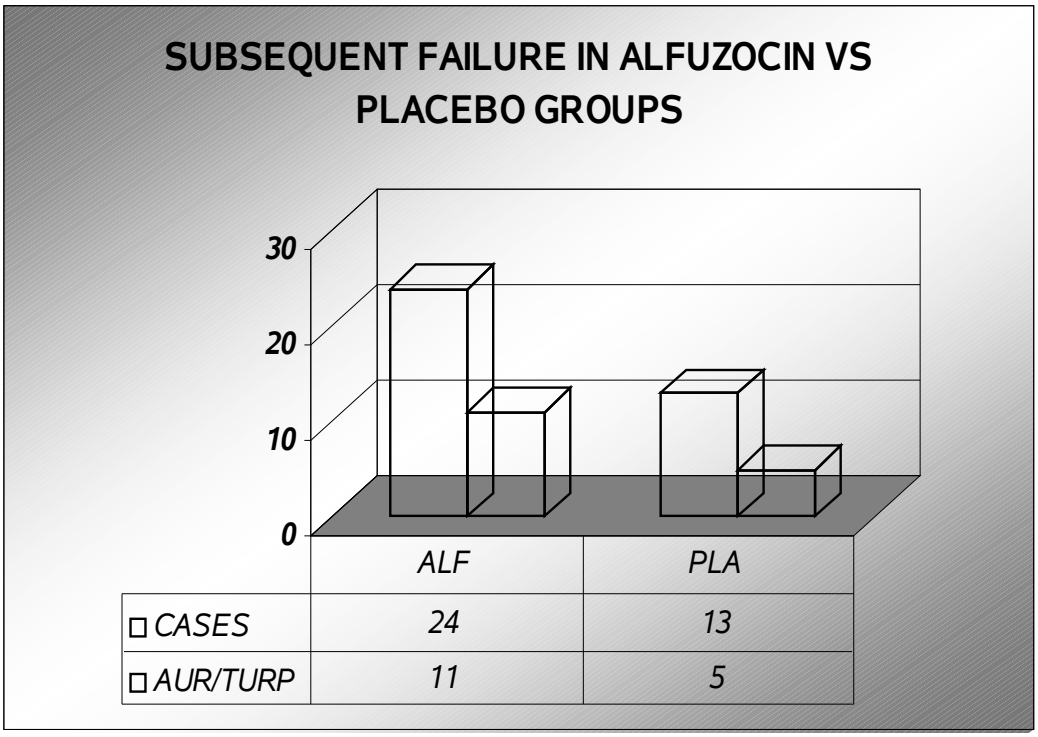
Alfuzosin (10 mg) once daily was well tolerated. Four patients in the SR alfuzosin treatment group experienced adverse events, while no adverse events were reported in the placebo group. Three patients experienced dizziness and one developed a headache, and all resolved with no treatment. None interfered with the continuation of the study.

RESULTS OF FOLLOW-UP

The failures during follow-up of the 43 patients who had a successful TWOC were defined as a subsequent occurrence of AUR and/or of bladder outlet surgery. Among the 43 patients who had a successful TWOC, six failed to attend their follow-up appointment. For the other 37 patients the mean (range) follow-up was 7.6 months (3 days–13 months). 16 patients experienced subsequent episodes of AUR or have undergone prostatectomy (TURP) with a mean interval from discharge after the successful TWOC of 4.2 months (range 3 days to 8.5 months). Two died at 5 and 9.5 months of follow-up for some other causes with no further intervention. Overall, 19 patients (44%) have had no subsequent episodes of AUR and continue to void satisfactorily.

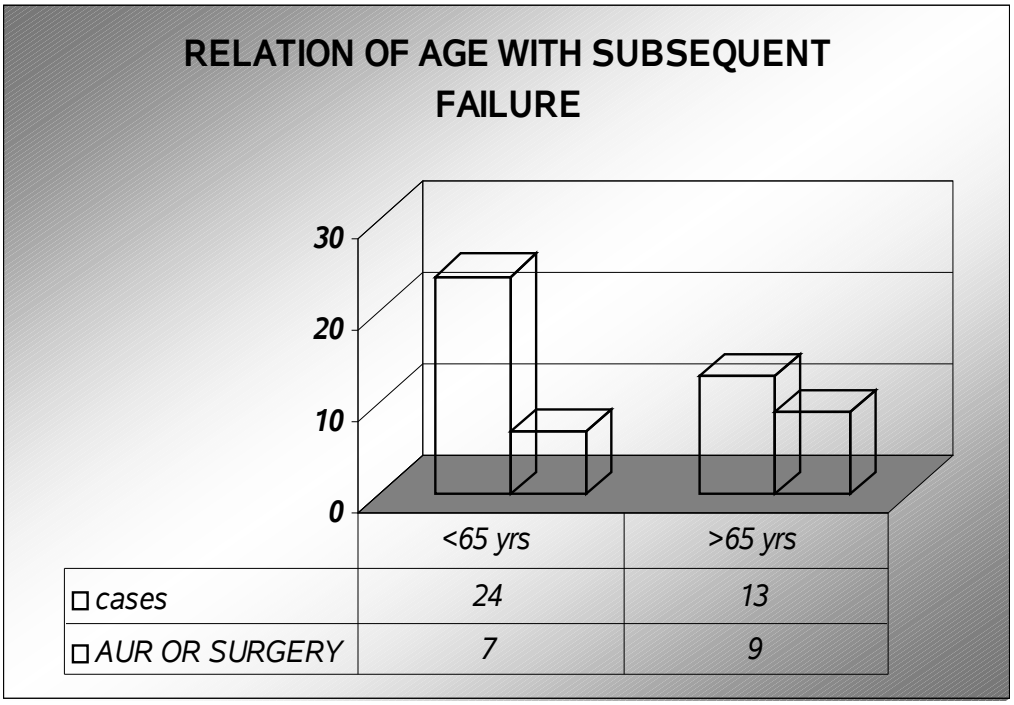


11 out of 24 successful cases in the Alfuzocin group on follow-up subsequently developed AUR or underwent TURP. 5 cases out of 13 in the placebo group went for recurrent AUR or TURP. Here the P value is 0.66 and Odds ratio is 1.35 (95% C.I 0.28-6.69) which is statistically not significant. So, initial doses of Alfuzocin may not be helpful in preventing subsequent failure.



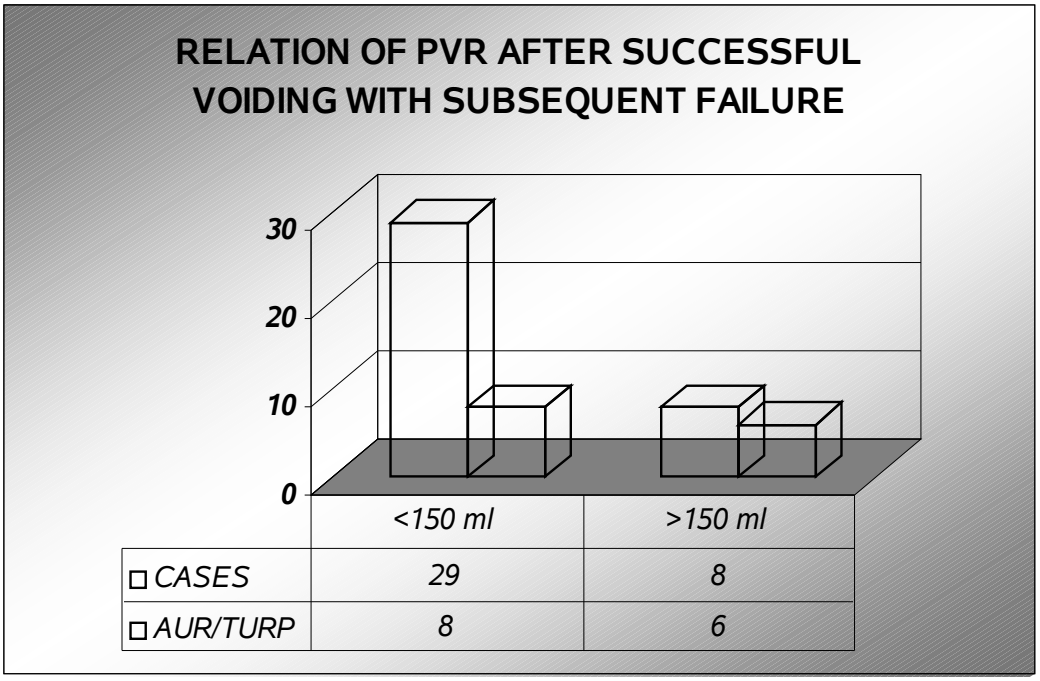
P value - 0.66 & Odds ratio - 1.35

Elderly patients (65 years or older) had significantly greater chances of subsequent failure (recurrent AUR or Surgery). 7 out of 24 successful cases in <65 years group & 9 out of 13 cases in >65 years age group developed recurrent AUR or required surgery for BPH during follow-up. Here P value is 0.019 which translates into Odds ratio of 5.46 (95% CI 1.03 – 31.71). So the relation between the age and subsequent failure is statistically significant.



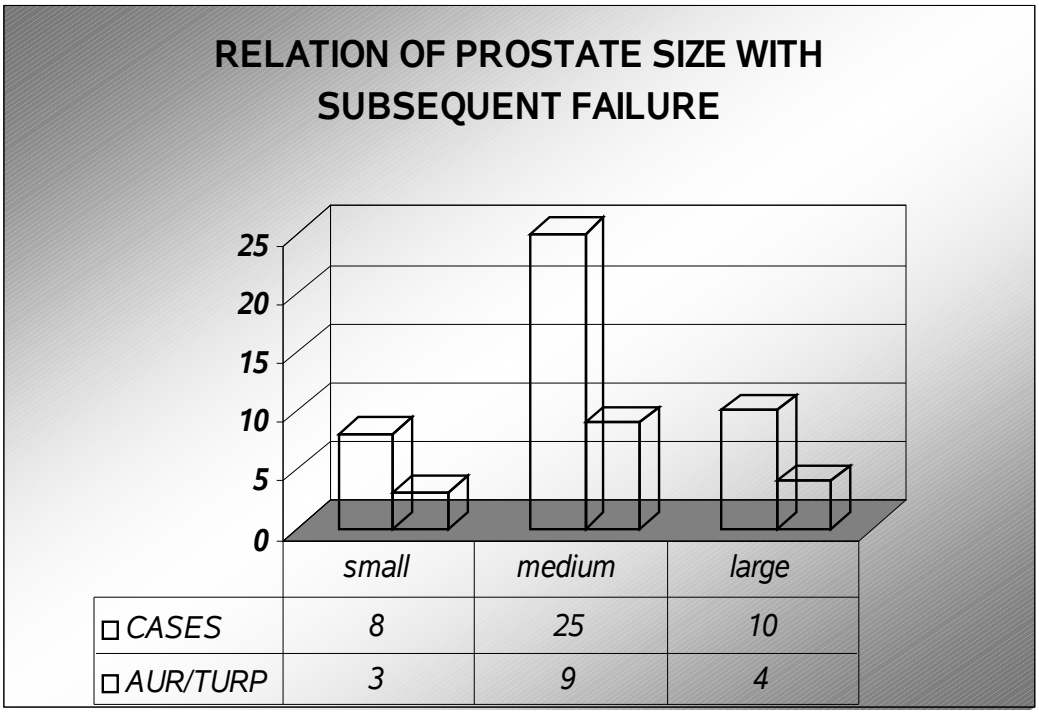
P Value – 0.019 Odds ratio – 5.46

Post void residual volume (PVR) was assessed by ultrasonography for those who had a successful TWOC. Six of eight patients who had a PVR of >150 ml required outflow tract surgery(TURP) or developed subsequent AUR and Ten of 29 patients who had a PVR of <150 ml have required bladder outlet surgery or developed further episode of AUR, the difference being statistically significant (P value is 0.03). This translates into an odds ratio of 0.16 (95% CI 0.02–1.14).



P Value – 0.03 Odds ratio – 0.16

No other factors were identified to date as being prognostic of the subsequent need for TURP. Prostate size categorized as small (≤20 g), medium (21–50 g) or large (≥51 g) on a DRE and abdominal USG by the admitting urologist was not associated with a statistically significant trend. (P value 0.98)



P value 0.98

Of all of the other factors examined only the post void residual volume (PVR) after a successful TWOC and advanced age (>65 years) approached statistical significance, those with above 65 years & residuals of >150 ml being more likely to fail during the follow-up.

DISCUSSION

Historically, the standard management of a man presenting with AUR caused by BPH was early prostatectomy, as it was assumed that the patient was presenting late in the natural history of their BOO. However, a study reporting the urodynamic assessment of men presenting with AUR showed that up to 23% did not require prostatectomy . Furthermore, it is recognized that patients undergoing TURP with a urinary catheter insitu are at a greater risk of peri- and postoperative complications.

Therefore it is common practice to undertake a TWOC after an episode of AUR. As previously reported, the success rate of this TWOC is significantly improved by giving an α-blocker such as alfuzosin . By examining the fate of a cohort of men who have had a successful TWOC it is possible to assess whether the AUR event is indeed the culmination of a slow decline associated with BPO.

An alternative hypothesis is that AUR is truly an acute event, of uncertain cause, associated with a sudden decompensation of the detrusor or increase in bladder outlet resistance. This being so it is possible that α-blockers and a period of catheter drainage, allowing inflammation to settle, would improve the outcome of a TWOC. Available evidence seems to support both hypotheses, indicating that several different causal factors may result in the development of AUR

The primary objective of the present study was to evaluate the efficacy of Alfuzocin compared with placebo for treating catheterized patients with AUR caused by BPH, by comparing those voiding successfully after removing their catheter. The definition of ‘success’ in the treatment of AUR has yet to be universally agreed. For patients it must, at least in part, relate to the lack of need for re-catheterization.

In the absence of any internationally agreed outcome measures for the success of a TWOC, TWOC was considered successful if the patient returned to satisfactory voiding (defined as a flow rate of > 5 ml/s, >125 ml voided volume, and a residual volume of ≤ 250 ml). These definitions are regarded as a reasonable reflection of successful bladder emptying; and deemed a failure if re-catheterization was required within 24 hours. This criteria is used in 2 similar studies. (Malcolm G. Lucas et al)[10]

This study shows that patients receiving SR alfuzosin were about two times more likely to void successfully than those who received placebo. The success rate of TWOC in the placebo group of 25% is of the same order of magnitude as that reported in previous uncontrolled observational studies. SR alfuzosin gave a significantly better outcome than placebo. 28 patients who received SR alfuzosin and 15 who received placebo did not require re-catheterization (47% vs. 25% success, $P = 0.011$; odds ratio 2.47, 95% CI 1.23–4.97).

Similar study by McNeill SA, Daruwala PD, Mitchell IDC, Shearer MG, Hargreave TB. Sustained-release alfuzosin and trial without catheter after acute urinary retention: a prospective, placebo-controlled trial. BJU Int 1999; 84: 622–7 In this study after removal of the catheter, 42% of patients voided successfully, 22 of 40 (55%) with SR alfuzosin and 12 of 41 (29%) with placebo (P=0.03). [40]

Tamsulosin in the management of patients in acute urinary retention from benign prostatic hyperplasia, a study conducted by Malcolm G. Lucas et al published in BJU International Volume 95 Page 354 - February 2005.In that study 149 men (mean age 69.4 years) were randomly assigned to receive tamsulosin (75) or placebo (74); eight were not evaluable, so the intent-to-treat population was 141 men. Thirty-four men taking tamsulosin and 18 taking placebo did not require re-catheterization on the day of the trial without catheter

(48% and 26% respectively, $P = 0.011$; odds ratio 2.47, 95% confidence interval, CI, 1.23–4.97) [10]

In the present study it was apparent that increasing age was associated with less likelihood of a successful TWOC; indeed, no patient over 80 years old voided successfully. This finding reflects recent reports that increasing age is a risk factor for AUR, failure of TWOC after AUR and poor outcome after surgery. This risk of AUR and poor outcome of TWOC and surgery with increasing age may be related to the increasing incidence of prostatic obstruction associated with ageing and the age-related decline in detrusor contractility.

The size of the residual volume after AUR has been reported to affect the chances of a successful return to voiding. According to Taube and Gajraj, a TWOC should be avoided if the residual volume is >900 ml. [4] Similarly,Djavan et al. found that a residual of <1 L was associated with a good chance of successful voiding after catheter removal, but recommended a period of prolonged catheterization if the volume was >1.3 L. [34]

In our study totally 32 cases out of 72 (44%) in both groups with urine volume of initial catheterization (Residual volume of AUR) <900ml voided successfully. But only 11 out of 48(23%) cases with initial catheterization volume >900ml had success in TWOC (P value-0.02, odds ratio 2.69).The Residual volume of AUR affect the outcome in our study similar to other studies. But McNeil in his study found the residual volume had no effect on the outcome of the TWOC.[5]

Prostate size has also been identified as a risk factor for urinary retention and thus may be a useful indicator of outcome after retention. Kumar V, Marr C, Bhuvangiri A, Irwin P. A prospective study of conservatively managed acute urinary retention: prostate size matters. BJU Int 2000; 86: 816–9 shows prostate size affecting the success rate, but they assess the size by

means of TRUS. There was no difference in outcome that could be related to prostate size in the present study, possibly because prostate size was assessed by a DRE & abdominal USG in the emergency context, which is much less reliable than TRUS.[21]

The follow-up data revealed that 19 out of 37 of those who voided successfully (51%) required no further intervention within a mean follow-up of 7.2 months after an episode of AUR, with 16 of 37 (43%) experiencing a further episode of AUR and/or requiring a prostatectomy within this period. However, it is encouraging that so many patients remained free of intervention after a successful TWOC, as this permits time for a full assessment of these patients, which in turn may facilitate surgical intervention in the absence of a urinary catheter.

McNeill SA, Hargreave TB and Members of the Alfaur Study Group. Alfuzosin once daily facilitates return to voiding in patients in acute urinary retention. J Urol 2004; 171: 2316–20 found 14 (17.1%) of the 82 alfuzosin-treated patients versus 20 (24.1%) of the 83 placebo-treated patients required BPH surgery, 5 (36%) of 14 versus 13 (65%) of 20 within 1 month, and 8 (57%) of 14 versus 17 (85%) of 20 within 3 months of treatment. Emergency surgery because of AUR relapse was the main cause of failure in both groups (11 [78.6%] of 14 in the alfuzosin group and 16 [80.0%] of 20 in the placebo group). [5]

In their study, compared with placebo, alfuzosin improved the Kaplan-Meier survival rates by 9.6% (P = 0.04), 11.4% (P = 0.04), and 8.3% (P = 0.20), with surgical risk reductions of 61%, 52%, and 29% at 1, 3, and 6 months of treatment, respectively. High prostate-specific antigen values and the post-TWOC residual urine volume significantly increased the risk of AUR relapse and BPH surgery. They recommend Alfuzosin 10 mg OD increased the likelihood of successful TWOC in men with a first episode of spontaneous AUR and should be continued beyond the acute phase, as it reduced the need for BPH surgery during a 6-month treatment

period.

But in our study 11 out of 24 successful cases in the Alfuzocin group on follow-up subsequently developed AUR or underwent TURP. 5 cases out of 13 in the placebo group went for recurrent AUR or TURP. Here the P value is 0.66 and Odds ratio is 1.35 (95% C.I 0.28-6.69) which is statistically not significant. So, initial doses of Alfuzocin may not be helpful in preventing subsequent failure. But we are not putting Alfuzocin in the follow-up period.

Elderly patients (65 years or older) had significantly greater chances of subsequent failure (recurrent AUR or Surgery).7 out of 24 cases in <65 years group & 9 out of 13 cases in >65 years age group developed recurrent AUR or required surgery for BPH. . Here P value is 0.019 which translates into Odds ratio of 5.46 (95% CI 1.03 – 31.71). So the relation between the age and subsequent failure is statistically significant.

McNeill SA, Rizvi S, Byrne D. Prostate size influences the outcome after presenting with acute urinary retention. *BJU Int* 2004;94: 559–62 In this study, those with larger prostates are most at risk of recurrent AUR or surgery after a successful TWOC, just as they are at higher risk of developing AUR initially. But in our study Prostate size categorized as small (≤20 g), medium (21–50 g) or large (≥51 g) on a DRE & USG by the admitting urologist was not associated with a statistically significant influence on the subsequent failure in the follow-up period.(P value = 0.98). [36,40]

Post void residual volume (PVR), of those who had a successful TWOC is considered as an important prognosticator of subsequent failure in many studies. Six of eight patients who had a PVR of >150 ml required outflow tract surgery(TURP) or developed subsequent AUR ,Ten of 29 patients who had a PVR of <150 ml have required bladder outlet surgery or developed further episode of AUR, the difference being statistically significant (P=0.03).

Of all of the other factors examined only age and the post void residual volume (PVR) after a successful TWOC approached statistical significance, Older age (>65 years) and those with residuals of >150 ml being more likely to fail during the follow-up. No other factors were identified to date as being prognostic of the subsequent need for TURP.

The distribution of patients was equal in both study groups, and so is unlikely to have affected the analysis of whether the treatment effects of Alfuzocin differ from those of a placebo. The safety profile was as expected for an alpha blocker, only 4 patients had mild dizziness and head ache.

Many questions remain unanswered about the use of alpha blockers in the clinical setting. It is still not possible to predict which patients are likely to respond to a-blockers and which are not; the study was not powerful enough to answer this. There were also insufficient data to draw conclusions about long-term outcomes for patients treated with SR alfuzosin. Published data from untreated patients suggested that many will require recatheterization or surgical intervention; 84% had surgery within 5 years in one study.

It would be valuable to study the long-term use of SR alfuzosin after catheterization for AUR. Works with another a-blocker, Tamsulocin, shows that treatment for 6 months was associated with a significantly lower incidence of de novo AUR than with placebo (0.4% vs. 2.4%). A retrospective analysis of five studies of the long-term use of alpha blockers for treating BPH showed that the incidence of AUR was significantly lower in patients taking this group of drugs, and there was a possible reduction in the need for surgery. From those results, SR alfuzosin can also be recommended for treating patients after catheterization for AUR, and can significantly reduce the likelihood of the need for re-catheterization.

A large-scale, randomized, double-blind, placebo-controlled, trial of long-term duration

is required to determine whether a medical therapy prevents urinary retention. Unfortunately, no randomized, double-blind, placebo-controlled studies of α blockers exceed 1 year of active treatment. Because men with large prostates have a threefold greater chance of developing urinary retention (Jacobsen et al, 1997), enrolling men with large prostates would enhance the probability of observing an effect on urinary retention. The 3-year open-label prospective study of alfuzosin supported a 0.3% risk of retention (Lukacs et al, 2000). This is markedly lower than the predicted risk of developing urinary retention in an age-matched cohort of men (Jacobsen et al, 1997). [15]

The MTOPS study is a 7-year placebo-controlled trial of 2800 men designed to determine the impact of medical therapy (placebo, doxazosin alone, finasteride alone, and combination therapy) on disease progression. This study will determine the impact of α blockers on preventing urinary retention.

CONCLUSION

In conclusion, this study provides evidence from a randomized double-blind placebo controlled trial that an alpha-blocker, SR alfuzosin, is useful in the management of AUR related to BPH. This study shows that patients receiving SR alfuzosin were about twice more likely to void successfully than those who received placebo. In addition, it provides further evidence that the patient age (>70 years) and residual volume of AUR (>900ml) are the factors significantly affecting the outcome.

While treatment with a1pha blockers may not obviate the need for surgery in all men who present with AUR, a reduction in the numbers being sent home with urinary catheters in situ is of benefit, as it may reduce subsequent perioperative morbidity and mortality, and it is more comfortable and convenient for the patients.

It is clear that certain measurable parameters like advanced age and large PVR after a successful TWOC (> 150ml) may be used to identify patients at highest risk of a further episode of AUR after initial success at TWOC, who may then be offered early operative intervention.

MASTER CHART

	AGE	PROSTATE SIZE	RESIDUAL VOLUME OF AUR	ALF/PLA	SUC/FAIL	PVR IN SUCCESSFUL PATIENTS	FOLLOW UP	FOLLOW UP RESULT
1	54	medium	600	A	S	120	13 Months	Voiding
2	67	medium	700	A	S	180	2.5 months	AUR
3	65	large	1100	A	F			
4	75	large	1200	A	S	190	3 days	AUR
5	60	medium	700	P	F			
6	66	medium	1400	P	F			
7	63	small	800	P	F			
8	80	medium	700	P	F			
9	62	small	700	A	S	180	lost to follow up	
10	62	medium	700	A	F			
11	58	medium	600	P	F			
12	63	medium	900	P	S	100	9 months	Voiding
13	73	medium	700	P	F			
14	53	small	500	A	F			
15	66	small	650	A	S	120	9.5 months	AUR
16	65	medium	950	A	F			
17	74	large	1200	A	F			
18	53	medium	950	P	F			
19	70	medium	700	P	F			
20	82	large	1300	P	F			
21	66	medium	950	A	S	100	11 months	Voiding
22	70	medium	800	A	S	60	lost to follow up	
23	62	small	850	P	F			

	AGE	PROSTATE SIZE	RESIDUAL VOLUME OF AUR	ALF/PLA	SUC/FAIL	PVR IN SUCCESSFUL PATIENTS	FOLLOW UP	FOLLOW UP RESULT
24	65	medium	900	P	F			
25	59	medium	700	A	F			
26	54	small	500	P	F			
27	63	large	1000	P	F			
28	55	medium	750	A	S	130	10.5 months	Voiding
29	56	medium	600	A	S	150	lost to follow up	
30	58	medium	850	A	S	110	7 months	TURP
31	59	medium	950	A	S	60	8.5 months	AUR
32	68	large	650	A	S	190	21 days	TURP
33	67	small	600	A	S	50	12 months	Voiding
34	64	large	800	A	S	110	7.5 months	Voiding
35	80	medium	650	A	F			
36	57	medium	500	P	F			
37	66	small	700	P	S	50	8 months	TURP
38	69	medium	900	P	F			
39	68	large	1100	P	F			
40	52	medium	500	A	S	120	9 months	Voiding
41	53	small	550	A	F			
42	65	medium	1100	A	F			
43	78	medium	1000	A	F			
44	54	medium	550	P	F			
45	70	medium	600	P	F			
46	79	large	1000	P	F			
47	81	large	1100	P	F			
48	54	medium	800	A	S	120	3 months	AUR

	AGE	PROSTATE SIZE	RESIDUAL VOLUME OF AUR	ALF/PLA	SUC/FAIL	PVR IN SUCCESSFUL PATIENTS	FOLLOW UP	FOLLOW UP RESULT
49	54	large	600	A	F			
50	52	medium	900	A	F			
51	71	large	1300	A	S	160	6months	AUR
52	55	small	950	P	F			
53	71	medium	550	P	S	100	death	
54	55	small	500	A	S	100	7 months	AUR
55	55	medium	1200	A	F			
56	82	medium	700	A	F			
57	63	large	800	P	S	150	6 months	Voiding
58	74	medium	1000	P	F			
59	53	medium	550	A	S	130	5 months	TURP
60	56	large	1400	A	F			
61	63	large	1400	A	F			
62	81	medium	1100	A	F			
63	53	large	600	P	S	180	3 months	TURP
64	62	small	1200	A	S	110	9 months	AUR
65	53	medium	550	P	S	60	9.5 months	Voiding
66	61	medium	750	A	S	120	7 months	Voiding
67	73	medium	900	A	S	120	lost to follow up	
68	52	small	500	P	S	140	4 months	Voiding
69	66	medium	1100	P	S	140	3 months	AUR
70	52	medium	950	P	S	70	5 months	Voiding
71	54	medium	500	P	S	100	lost to follow up	
72	67	medium	600	P	F			

	AGE	PROSTATE SIZE	RESIDUAL VOLUME OF AUR	ALF/PLA	SUC/FAIL	PVR IN SUCCESSFUL PATIENTS	FOLLOW UP	FOLLOW UP RESULT
73	58	small	1200	A	F			
74	67	medium	950	A	F			
75	60	small	950	P	F			
76	67	medium	950	P	S	100	2.5 months	AUR
77	68	medium	1000	P	F			
78	76	large	1200	P	F			
79	73	medium	600	P	F			
80	55	small	600	A	S	110	6 months	Voiding
81	62	large	700	A	S	140	5 months	Voiding
82	64	medium	1000	A	S	110	death	
83	63	large	1200	A	F			
84	55	medium	1000	P	S	50	lost to follow up	
85	58	medium	900	P	F			
86	63	small	800	P	F			
87	62	small	700	P	F			
88	61	medium	1200	P	F			
89	76	large	900	P	F			
90	57	large	650	A	S	190	4 months	Voiding
91	54	medium	550	A	F			
92	61	medium	600	A	S	110	6 months	Voiding
93	61	large	1000	A	F			
94	76	medium	800	A	F			
95	52	medium	600	P	F			
96	74	medium	1300	P	F			
97	64	medium	900	A	S	100	5 months	Voiding

	AGE	PROSTATE SIZE	RESIDUAL VOLUME OF AUR	ALF/PLA	SUC/FAIL	PVR IN SUCCESSFUL PATIENTS	FOLLOW UP	FOLLOW UP RESULT
98	62	small	550	A	F			
99	80	large	700	A	F			
100	67	medium	700	P	S	180	4.5 months	AUR
101	64	medium	600	P	F			
102	76	large	950	P	F			
103	60	large	1200	A	F			
104	68	medium	700	P	F			
105	78	medium	1100	P	F			
106	82	large	1200	P	F			
107	60	medium	800	A	F			
108	76	large	1100	A	F			
109	56	large	600	P	S	100	5 months	Voiding
110	62	medium	1200	P	F			
111	62	small	1300	A	F			
112	75	large	500	A	F			
113	65	large	1100	P	F			
114	61	medium	1300	P	F			
115	56	medium	600	P	F			
116	72	large	1300	P	S	180	3 months	Voiding
117	67	medium	500	A	F			
118	76	large	600	A	F			
119	55	medium	1200	P	F			
120	64	large	700	P	F			

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